ORIGINAL RESEARCH

Inflammatory markers in lean Polycystic Ovary Syndrome subjects are not associated with the spectrum of dyslipidemia

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ABSTRACT

Objectives: This study aimed to address the detailed lipid profile in lean woman with PCOS and investigate the relationship between chronic low grade inflammation (using NLR, PLR, and monocyte/HDL ratio) and dyslipidemia (defined as total cholesterol level > 190 mg/dL).

Materials and Methods: This study was a cross-sectional study conducted from June – December 2020 at the Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, involving 45 women aged 18 – 35 years old, diagnosed as having PCOS with normal BMI (18.5 – 22.9 kg/m^2). To compare quantitative variables, data analysis was carried out using the t-test or Mann-Whitney U test as appropriate; whereas, to compare categorical variables, the Chi-square test was used.

Results: We found that although the median BMI was within normal limits at 21.48 kg/m^2, the mean values of the lipid profiles were found to be either abnormal or borderline, indicating the high possibility of dyslipidemia. No statistically association between NLR, PLR and MHR with dyslipidemia.

Conclusion: Dyslipidemia and chronic low-grade inflammation were found in lean PCOS subjects, but there was no significant association between inflammation markers (NLR, PLR and MHR) and dyslipidemia. Further studies should investigate other factors that cause the inflammation.

Keywords: dyslipidemia; inflammation; lean PCOS; maternal health

ABSTRAK

Tujuan: Tujuan dari penelitian ini adalah untuk mengetahui profil lipid pada pasien SOPK non obesitas dan mencari tahu hubungan antara inflamasi kronis derajat rendah (RNL, RPL, rasio monosit/HDL) dan dislipdemia (kadar kolesterol > 190 mg/dL)

Bahan dan Metode: Studi *cross sectional* dilakukan dari Juni – Desember 2020 di Departemen Obstetri Ginekologi Fakultas Kedokteran Universitas Indonesia, Jakarta, Indonesia, melibatkan 45 wanita berusia 18-35 tahun yang terdiagnosis SOPK dengan IMT normal (18.5 – 22.9 kg/m^2). Data kuantitatif dihitung dengan menggunakan uji T dan uji Mann-Whitney U sedangkan data kategorik menggunakan uji Chi-square.

Hasil: Meskipun IMT dalam batas normal, rata-rata kadar lipid pada pasien ditemukan abnormal atau batas tinggi, yang menunjukkan adanya kemungkinan dislipidemia. Tidak ditemukan adanya hubungan signifikan antara NRL, PLR, dan MHR dengan dislipidemia.

Simpulan: Dislipidemia dan inflamasi kronis derajat rendah ditemukan pada pasien SOPK non-obesitas, tetapi tidak ditemukan hubungan signifikan antara marka inflamasi (NLR, PLR, dan MHR) dengan dislipidemia. Penelitian selanjutnya diperlukan untuk mengetahui faktor lain yang terkait kondisi inflamasi kronis derajat rendah.

Kata kunci: dislipidemia; inflamasi; SOPK non-obes; kesehatan ibu

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrine problem mostly seen in reproductive age women, around 5 to 10% as concluded from the European Society for Human Reproduction and Embryology/ American Society for Reproductive Medicine (ESHRE/ASRM) in 2004.[1] PCOS patients have abnormal anthropometry profile, more than 80% have obesity body mass index (50-80%), however the disease can also be found in women with normal body mass index (20-50%). PCOS contributes to the quality of life that can change the endocrine and metabolic body process. Factors associated with this syndrome include glucose intolerance, abnormal blood lipid levels, insulin resistance, oxidative stress and other metabolic abnormalities, and among these abnormalities, dyslipidemia is one of the most common phenomena observed in women with PCOS.[2,3] In most cases, dyslipidemia indicates an abnormal serum lipid component (at least one component) (i.e. high total cholesterol (> 190 mg/dL), high triglycerides, high Low Density Lipoprotein (LDL), and low High Density Lipoprotein (HDL)).[4]

Until now, it is not yet known the exact etiology and pathogenesis of ovarian polycystic syndrome both in obesity group or non-obesity group, the differences between those groups also have not been classified. One of the theories says that ovarian polycystic syndrome is a condition of chronic inflammation in low degree.[5] There are several markers that can be used to measure inflammation, including CRP, Neutrophil to Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), and monocyte/HDL ratio. Complete blood count is an inexpensive, routine, and feasible test that may provide information regarding the red blood cells, white blood cells, and platelets. Proinflammatory mediators (chemokines and cytokines) can be released by platelet, and, when activated, platelets can stimulate thrombus formation. The activation of platelets plays a crucial role in cardiovascular events and coronary artery disease as inflammation marker.[6,7] However, the data about PLR, NLR, and monocyte/HDL ratio and its association with inflammation and their correlation with dyslipidemia are lacking in PCOS patients. Therefore, this study aims to address the detailed lipid profile in lean woman with PCOS and investigate the relationship between chronic low grade inflammation (using NLR, PLR, and monocyte/HDL ratio) and dyslipidemia (defined as total cholesterol level > 190 mg/dL).

MATERIALS AND METHODS

This study was a comparative, observational, and cross-sectional study. The study was conducted from June until December 2020 at the Departments of Obstetrics and Gynecology of Universitas Indonesia and Human Reproductive, Infertility and Family Planning Research Centre, Indonesia Medical Education and Research Institute (IMERI), Faculty of Medicine Universitas Indonesia. Forty five women aged 18 – 35 years old, diagnosed as having PCOS with normal BMI (18.5 – 22.9 kg/m^2) were enrolled after giving informed consent. All the subjects enrolled in the study were in good health, had no chronic or acute disease, and for at least three months had not been taking any medication known to affect lipid profile.

For the basis of PCOS diagnosis, we used the revised Rotterdam criteria, in which that at least two of the these three features are required: (1) oligo-ovulation or anovulation (< 6 menstrual periods per year); (2) clinical and/or biochemical signs of hyperandrogenism, including hirsutism (Ferriman-Gallwey score > 8), severe persistent acne, and/ or total testosterone level > 0.8 ng/mL); and (3) sonographic evidence of PCOS (i.e., at least one ovary containing 12 or more peripheral follicles measuring 2–9 mm in diameter and/or ovarian volume of at least 10 mL).

Exclusion criteria were patients with acute infection, history of cancer, autoimmune disease, hematologic disease, chronic disorders (diabetes mellitus, renal, heart or liver disorder), patients who have endocrine disorders (hyperprolactinemia, nonclassical congenital adrenal hyperplasia), use of any antidiabetic, antiobesity, anti-inflammatory and hormonal drugs (oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents) within the previous two months.

We performed a detailed medical history taking and full clinical examination for all participants. The data that we recorded included age, menstrual pattern, and history of significant metabolic or cardiac disease. For physical examination, we measured the weight, height, and blood pressure as well as the body mass index (BMI, calculated as weight in kilograms divided height in meters squared). Waist circumference was defined as the obtained minimum circumference value of the iliac crest and lateral costal margin.

For the measurement of total cholesterol, high and low density lipoprotein (HDL and LDL), fasting blood glucose, and triglycerides levels, the blood samples were taken between 7 a.m. – 10 a.m. with an overnight fasting. Lipid levels measurement was carried out using enzymatic assay kits. The glucose oxidase method was performed to measure the glucose level.

Based on World Health Organization (WHO) estimates in 2008, dyslipidemia is defined as total cholesterol blood levels of > 5 mmol/L (190 mg/dL) in the

Southeast Asia. Patients were then divided into two group based on total cholesterol level.

The data were reported as mean ± SD or number and percentage. The t-test or Mann-Whitney U test was used to compare of quantitative variables. For the comparison of categorical variables, we performed the Chi-Square test (except for a less than 5 frequency, in which we used the exact test). A P value of ≤ 0.05 was considered significant. Data analysis was carried out using the Statistical Package for the Social Sciences, version 15 (SPSS, Chicago, IL, USA).

RESULTS AND DISCUSSION

In this study, 45 lean PCOS women were included. Table 1 shows the clinical and biochemical characteristics of lean women diagnosed with PCOS. We found that although the median BMI was within normal limits at 21.48 kg/m^2, the mean values of the lipid profiles were found to be either abnormal or borderline, indicating the high possibility of dyslipidemia. Furthermore, we found that there is no significant association between changes in the inflammation markers (NLR, PLR and Monocyte/HDL ratio) and dyslipidemia (p > 0.05) as shown in Table 2.

In this study, despite the lean women having a normal body mass index, the lipid profiles of the women were either abnormal or borderline with mean HDL cholesterol 52.88 mg/dL, LDL cholesterol 121.71 mg/dL and total cholesterol 196.73 mg/dL. This finding is consistent with the National Cholesterol Education Program guidelines which suggest that about 70% of women with PCOS exhibit borderline or high lipid levels. According to the same guideline, criteria for metabolic syndrome includes the low level of HDL <50 mg/dL showing that our finding suggests a borderline low level of HDL of 52.88 mg/dL. This result is consistent with most previous studies showing a reduced level of HDL in women with PCOS.[8,9] The findings on our study showed a relatively higher HDL compared to other studies possibly due to the exclusion of obese PCOS in our study, unlike many others which included both obese and lean patients. The exact mechanism behind reduction of HDL in women is poorly understood. However, one hypothesis suggests that the reduction in HDL occurs due the underlying insulin resistance and hyperandrogenemia, which are thought to enhance the activity of hepatic lipase, removing lipid from HDL, consequently reducing the number of HDL particles.[10]

Table 1. The clinical and biochemical characteristics of lean women with PCOS (n=45).

Variable	Mean ± SD	Median (range)
Age	28.60 ± 3.68	
Weight (kg)	53.61 ± 4.96	
Height (cm)	159.7 ± 5.46	
BMI (kg/m^2)		21.48 (17.97 – 22.72)
Fasting blood glucose		87.9 (70.2 – 151)
HDL cholesterol	52.88 ± 10.39	
LDL cholesterol	121.71 ± 32.78	
Total cholesterol	196.73 ± 39.42	

Table 2. The association between changes in inflammation markers (NLR, PLR and Monocyte/HDL ratio) and dyslipidemia (total cholesterol > 190 mg/dL).

Inflammation Marker	Dyslipidemia	No Dyslipidemia	Total	P value
NLR				
High ($\geq$ 1.60)	12 (52.2)	13 (61.9)	25 (56.8)	0.515[a]
Low (<1.60)	11 (47.8)	8 (38.1)	19 (43.2)	
PLR				
High ($\geq$ 11.50)	2 (8.3)	3 (14.3)	5 (11.1)	0.526[a]
Low (<11.50)	22 (91.7)	18 (85.7)	40 (88.9)	
Monocyte/HDL ratio				
High ($\geq$ 11.46)	4 (16.7)	6 (28.6)	10 (22.2)	0.338[a]
Low (<11.46)	20 (83.3)	15 (71.4)	35 (77.8)	

Values are presented in number (percentage), [a]Chi-square

In terms of LDL, our study showed an increased level of LDL at borderline level. This finding is in line with previous studies which have also shown marked increase in LDL amongst women with PCOS, even in lean patients.[11] A retrospective study in Rome also reported a non-significant difference in LDL levels between obese and lean women diagnosed with PCOS, showing that an increased level of LDL seems to be a common finding in women with PCOS regardless of their BMI.[12] In contrast, a study in Korea found that no significant change was found in the level of LDL in non-obese Korean patients.[11] The differences in the these findings of lipid profile may be explained by differing phenotypes of the PCOS, which we did not take into account in this study. This phenomenon is supported by a study by Spalkowsa et al. who suggested that different lipid profiles may be found in PCOS based on its phenotypes and androgens' levels.[13] It is also worth noting that, aside from LDL quantity, recent studies have also suggested that the quality of LDL is affected in PCOS. In PCOS, smaller and denser LDL particles, which are more atherogenic, are more commonly found.[10,14-17]

As for total cholesterol, our study has also shown that, even in lean patients, there seems to be an increased level of total cholesterol. This is in agreement with a previous Danish study which has also found increased median values of total cholesterol in PCOS subjects.[18] In lean patients, increased level of cholesterol is still possible due to intraabdominal visceral fat accumulation, hyperandrogenemia, and insulin resistance, all of which result in abnormalities in lipid metabolism. Interestingly, another study also found that family history of dyslipidemia results in higher values of total cholesterol.[10] This genetic component can potentially be a confounding variable, which was not taken into consideration in this study.

The presence of dyslipidemia found in this study prompts further question regarding its association with low grade, chronic inflammation as its possible underlying cause in lean PCOS patients. Chronic low-grade inflammation has been thought to be one of the pathological mechanisms affecting women with PCOS. The inflammation is likely to be associated with insulin resistance, endothelial dysfunction and atherosclerosis, caused by increased visceral adiposity, which appears to occur regardless of BMI.[19] However, this study has also found that there is no significant association between changes in the inflammation markers (NLR, PLR and Monocyte/HDL ratio) and dyslipidemia in the patients (p > 0.05). This finding is not in line with previous studies which found their association with PCOS patients. A study by Cakiroglu et al. has shown that both NLR and PLR were significantly increased in all PCOS patients.[20] Another study by Pergialiotis et al. found that

NLR and PLR were not affected by obesity, hence similar results should be produced even with lean women populations.[21] Nevertheless, the study by Cakiroglu et al. did not investigate the correlation between NLR and PLR with lipid profile indices.[20] In fact, the study by Pergialiotis et al. found weak correlation (r = -0.171), between NLR and HDL values.[21]

Similarly, in terms of monocyte/HDL ratio (MHR), our finding is not in agreement with prior study by Usta et al. in 124 women which found that MHR may be a novel and useful predictor of the presence of PCOS (P = 0.0018). The study also recommended the use of MHR as a low-cost, reproducible marker to detect cardiovascular risk in PCOS patients. However, in this study, it was not clear if MHR had any direct correlation with dyslipidemia (measured by cholesterol), although it was indicated that there was a significant difference in total cholesterol level between their PCOS subjects and non-PCOS subject (P = 0.022).[22] The differences between our findings and the previous study may be attributed to the small number of samples used in our study. Moreover, our study involved only lean patients who are thought to suffer less severe hormonal and metabolic derangements compared to their obese counterparts.[4]

The strength of our study is that this is the first study investigating direct association between inflammation markers NLR, PLR and MHR with dyslipidemia in PCOS patients. Our limitation is the small number of subjects enrolled in this study. Further investigation with larger number of subjects is encouraged.

CONCLUSION

In lean PCOS subjects, we found that there are dyslipidemia and chronic low grade inflammation. In this study, we failed to find significant association between the inflammation markers (NLR, PLR and MHR) and dyslipidemia in our subjects, but we cannot rule out low-grade chronic inflammation as the probable cause of metabolic syndrome in lean PCOS women. We speculated that there might be other factors that can cause inflammatory condition, such as sedentary life style, poor nutrition, and dysbiosis of gut microbiota, so screening these women for metabolic abnormality like insulin resistance is recomm ended.

DISCLOSURES

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Conflict of Interest

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Author Contribution

All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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